



Hydroxycut hepatotoxicity: A case series and review of liver toxicity from herbal weight loss supplements

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Abstract

Dietary supplements represent an increasingly common source of drug-induced liver injury. Hydroxycut is a popular weight loss supplement which has previously been linked to hepatotoxicity, although the individual chemical components underlying liver injury remain poorly understood. We report two cases of acute hepatitis in the setting of Hydroxycut exposure and describe possible mechanisms of liver injury. We also comprehensively review and summarize the existing literature on commonly used weight loss supplements, and their individual components which have demonstrated potential for liver toxicity. An increased effort to screen for and educate patients and physicians about supplement-associated hepatotoxicity is warranted.

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INTRODUCTION

Obesity has become an increasingly important public health problem in the United States. Recent data show that more than 30% of adults are obese and 65% overweight^[1]. The use of dietary supplements for weight loss has become increasingly popular, as reflected by the \$55.4 billion spent in the U.S. in 2006 for weight loss and diet control^[2,3]. Based on a study by the National Center for Complementary and Alternative Medicine (NCCAM), 36% of adults are using some form of complementary or alternative medicine, which rises to 62% when including megavitamins or prayer. Although dietary and herbal supplements are governed under the DSHEA act of 1994, they are not presently regulated by the U.S. Federal Drug Administration, and the safety profiles of many are unknown. An increasing number of case reports have emerged which suggest causative supplement-associated liver toxicity. Hydroxycut is an herbal weight loss supplement that has been suspected to have possible liver toxicity. Herein we present two patients who experienced severe acute hepatitis in the setting of documented Hydroxycut exposure, and without alternative etiology after comprehensive serologic liver evaluation.

CASE REPORTS

Case 1

A 40-year-old female with a prior medical history notable only for hypothyroidism and diet-controlled hyperlipidemia presented to the Emergency Department with 3 d of new-onset crampy, mid-epigastric abdominal pain and non-bloody diarrhea. She noted subjective fevers and chills, and two isolated episodes of nausea and vomiting, anorexia and profound fatigue. She did not experience jaundice, icterus, pruritus, arthralgias, acholic stools or dark urine. One week prior to presentation, she began using Hydroxycut, 6 pills daily in preparation for a bodybuilding competition. Just prior to presentation she attended an office holiday party, although no other persons in attendance became ill. She did not smoke or drink. She otherwise does not take regular medications except for levothyroxine. She denied taking any other supplements or alternative medications. She was afebrile with stable vital signs, and normal body mass index. Her exam was notable only for mild mid-epigastric tender-

ness to palpation. She had no liver enlargement and no stigmata of chronic liver disease. Her laboratory profile on admission revealed an acute hepatitis with AST 1020 U/L and ALT 1150 U/L, total bilirubin 0.67 mg/dL, alkaline phosphatase 299 U/L, INR 0.96, white cell count $5.9 \times 10^3/\mu\text{L}$, hemoglobin 11.9 g/dL, platelet count 228/ μL , and creatinine 0.9 mg/dL. Diagnostic evaluation was negative for hepatitis A, B, C, cytomegalovirus and Epstein-Barr virus, autoimmune liver disorders (ANA, ASMA), alpha-1 anti-trypsin deficiency, and ehrlichiosis. On day 2 of admission, her transaminases decreased to AST 399 U/L and ALT 647 U/L. On day 3, she was clinically well and discharged from the hospital. Upon outpatient follow-up, she had returned to her usual state of health with normalization of transaminases with AST 46 U/L and ALT 48 U/L. She has not experienced any further recurrence of symptoms or liver abnormalities within 10 mo of follow-up.

Case 2

A 33-year-old female with a prior medical history of a pituitary adenoma presented to the Emergency Department with 1 mo of new-onset jaundice. She reported a flu-like illness of 2 wk duration with nausea and crampy abdominal pain and began to experience jaundice, acholic stools, dark-colored urine, pruritus, and profound fatigue. These symptoms appeared to be improving during the week prior to admission except for worsening jaundice and fatigue. She noted that during the month prior to admission, she had taken Hydroxycut supplements for 2 wk to help achieve weight loss, but discontinued this medication upon onset of symptoms. She additionally reported eating lobster during the month prior to admission, but could not recall other individuals who became ill. Her only medication was Ortho-Novum contraceptive, which she had been taking for 2.5 years. Her social history was unremarkable without regular alcohol ingestion, and the absence of risk factors for chronic viral hepatitis. She was afebrile with stable vital signs, and normal body mass index. Her exam was notable only for jaundice and scleral icterus. She had no liver enlargement and no stigmata of chronic liver disease. Her laboratory profile at admission was notable for acute hepatitis with AST 934 U/L and ALT 1570 U/L, total bilirubin 20.9 mg/dL, direct bilirubin 14.2 mg/dL, alkaline phosphatase 112 U/L, INR 1.08, white cell count $9.2 \times 10^3/\mu\text{L}$, hematocrit 42%, platelet count 414/ μL , creatinine 0.8 mg/dL. Diagnostic evaluation was negative for hepatitis A, B, C, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus infections. Her autoimmune profile revealed low titer increase in anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) suggestive of an immune-mediated drug-induced hepatitis. Her jaundice eventually resolved and her liver function normalized.

DISCUSSION

The public's increasing demand for alternative medicine, the newly found global interest in phytomedicine and herbal therapies, the rising cost of conventional

Table 1 Hydroxycut ingredients supplement facts (serving size 2 caplets)

Amount per serving	% daily value
Calcium (as hydroxycitrate) 156 mg	16 ¹
Chromium (as polynicotinate) 133 mg	111 ¹
Potassium (as hydroxycitrate) 218 mg	6 ¹
Garcinia Cambogia (66% hydroxycitric acid)	2
Gymnema Sylvestre (25% gymnemic acid)	2
Soy Phospholipids	2
Rhodiola rosea extract (5% rosavins)	2
Green Tea as Camellia Sinensis (91 mg of EGCG)	2
White Tea as Camellia Sinensis (15% EGCG)	2
Oolong Tea as Camellia Sinensis (15% EGCG)	2
Caffeine anhydrous	2

¹Percent daily values based on 2000 calorie diet; ²Daily values not established.

prescription drugs, and a loss of faith in Western medicine, have led to a rapid rise in the use of unregulated herbal supplements and therapies. An estimated 80% of the world population uses herbal medicines, largely outside the U.S.^[4] In a study performed at an outpatient liver clinic, over 21% of patients were taking herbal supplements in the setting of chronic liver disease^[5]. The FDA describes dietary supplements as a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet. The “dietary ingredients” in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Most of these products have not been rigorously studied through placebo-controlled, blinded, randomized trials^[6].

Hydroxycut is one of the most popular dietary supplements for weight loss on the market today, including two formulations Hydroxycut and Hydroxycut hardcore. Hydroxycut contains several different herbs, including: *Garcinia Cambogia* extract, chromium polynicotinate, *Gymnema sylvestre* extract and *Camellia Sinensis* (*C. Sinensis*) (Table 1). Both patients in this report used the dietary supplement Hydroxycut within a short time frame before presenting with acute hepatitis, suggesting Hydroxycut as the most likely etiology for acute liver injury. Neither patient had a history suggestive of other exposures or risk factors for viral hepatitis, alcoholic hepatitis, other toxin-mediated injury, or chronic liver disease. A comprehensive serologic and radiographic evaluation performed in both patients did not reveal alternative sources for liver toxicity. Although causation is difficult to confirm in cases of suspected drug-associated hepatotoxicity, the temporal relationship to acute liver injury and rapid resolution upon withdrawal of Hydroxycut make this likely. Hydroxycut has previously been associated with both a cholestatic and hepatocellular pattern of injury. The specific components likely implicated in liver toxicity include *G. Cambogia*, *Chromium*, and green tea root extract (*Camellia Sinensis*) based on prior data suggesting liver toxicity. Patient 1 experienced a more typical hepatocellular pattern of injury, patient 2 demonstrated an immune-mediated pattern of injury, which has not previously been described.

There has been one prior report of two cases of possible hepatotoxicity with Hydroxycut in the literature^[7]; both cases were young males who had documented periods of Hydroxycut exposure and experienced similar clinical syndromes marked by fatigue, jaundice, and pruritus with marked hepatocellular or cholestatic pattern and complete resolution upon supplement withdrawal. Our case series validates the likely causative relationship between Hydroxycut exposure and liver toxicity, and further suggests that an autoimmune pattern of hepatotoxicity may be observed. Although less common, drug-associated autoimmune hepatitis has been reported in several herbal supplements including Greater Celadine, Dai-Saiko-To, and Black Cohosh. Herein we review key ingredients of Hydroxycut that have been implicated in liver toxicity.

G. Cambogia is a fruit native to southeastern Asia and western Africa used to make meals more “filling”^[8]. Its main component hydroxycitric acid (HCA) is an inhibitor of the citrate cleavage enzyme (ATP citrate lyase) blocking de novo synthesis of fatty acids^[9]. HCA was initially studied in rodents for the dietary treatment of obesity and the results seemed to be promising. Unfortunately randomized controlled trials in humans for this purpose showed very conflicting results. Nevertheless, HCA is a primary component of many weight loss supplements in the market, and similar to others in its class, the toxicity profile is poorly studied. In the recent literature a case of fatal liver failure was reported in a patient taking HCA and montelukast suggesting the synergistic hepatotoxic effect of these two agents^[10]. There have also been reports of *G. Cambogia* toxicity by the WHO database, mostly describing an increase in hepatic enzymes^[6].

Chromium is an essential trace element and cofactor to insulin most commonly occurring in hexavalent (VI) and trivalent (III) states. The hexavalent form is found in the dye and leather industry and is responsible for occupational toxicity ranging from dermatitis to lung cancer^[11]. In 1989, the National Academy of Sciences established an “estimated safe and adequate daily dietary intake” range for chromium of 50 to 200 mg^[12]. In 2001 the Institute of Medicine and the National Academy of Sciences established Dietary Reference Intakes (DRI) for Chromium, ranging from 0.2 mg for infants to a maximum of 45 mg in lactating mothers^[13]. Chromium is used in weight loss supplements due to purported effects of decreasing body fat and increasing basal metabolic rate^[14,15]. A recent meta-analysis of available RCTs concluded that weight reduction with chromium although statistically significant was not clinically meaningful^[2]. There have been case reports of chromium toxicity causing acute hepatitis, thrombocytopenia and renal failure due to both environmental^[16,17] and dietary supplements^[18]. Although renal failure requiring dialysis is a more common concern^[19], those presenting with liver toxicity frequently elaborate aminotransferase elevations greater than 1000 mg/dL. Each Hydroxycut serving contains 133 mg of Chromium, which is taken three times daily, resulting in a cumulative daily consumption

greater than twice the NAS safe maximum dose.

Camellia Sinensis is the scientific name for green tea, which is widely regarded by the public as safe, and commonly incorporated into supplements due to purported anti-cancer potential^[20], weight reduction^[21] and antioxidant properties^[22]. Acute hepatotoxicity from *C. Sinensis* is well-described, and may range from acute hepatitis to acute liver failure. Based on 17 published cases in the literature^[23-27], most cases appear to occur following large ingestions of green tea, with resolution following withdrawal, and recurrence with re-challenge^[28]. Consequently, *C. Sinensis* has been banned in France and Spain, although it remains unregulated in weight loss supplements commercially available in the U.S.

Other Hydroxycut components for which liver toxicity have not been described include *Gymnema Sylvestre*, *Rhodiola Rosea*, and *Withania Somnifera*. *Gymnema Sylvestre* has been used to control hyperglycemia^[29] and hyperlipidemia^[30] in rats. Toxicity studies in rodents have not shown hepatotoxicity^[31] and no case report of liver injury has been reported. *Rhodiola Rosea* extract is used to decrease fatigue^[32] and improve exercise tolerance^[33]. *Withania Somnifera* has been used for its anti-inflammatory properties^[34,35]. Neither *R. Rosea* or *W. Somnifera* have been associated with liver toxicity, although *W. Somnifera* may result in renal impairment in rats^[36].

Of note, the more concentrated Hydroxycut Hard Core product contains additional herbal formulations such as White Willow extract and Yohimbine. These have not been demonstrated to result in liver injury, whereas Willow bark extract may have anti-inflammatory effects *in vitro*, this was not observed in patients with rheumatoid arthritis or osteoarthritis in a randomized controlled trial^[37]. Yohimbine is an indole alkaloid from the bark of the African *Pausinystalia Yohimbe*, and serves as an alpha-2 receptor antagonist which may treat male impotence^[38]. Although nausea, vomiting and abdominal pain have been described, liver toxicity has not been observed.

The FDA has issued warnings on several herbal supplements known to have hepatotoxic potential including Comfrey (2001), Kava (2002) and the dietary supplement Lipokinetix (2001). This review does not seek to provide a comprehensive review of all known hepatotoxins, but highlight a short list of ingredients within best selling weight loss supplements which have been demonstrated to have hepatotoxic potential.

Ephedra alkaloid, AKA *Ma Huang*, is the most commonly used weight loss supplement in the U.S.^[4], and is well-known to have potentially deleterious cardiovascular and CNS effects^[39], but has also been implicated in numerous cases of liver failure^[40,41]. As such, dietary supplements containing ephedra were banned in the U.S. in April 2004^[42], but remain widely available through unregulated internet sources in various forms, including the supplement *Leptoprin* (previously *Anorex*) which contains 20 mg of ephedrine, 200 mg of caffeine, 324 mg of aspirin, and unknown amounts of Green tea and cayenne. *Adipokinetix* came to the market to replace *Lipokinetix* which was removed in 2002 by Syntrex Innovations Inc. due to FDA

Table 2 Components of popular weight loss supplements

Brand name	Potentially hepatotoxic components
Hydroxycut	<i>Garcinia Cambogia</i> , Chromium, <i>Camelia Sinensis</i>
Ephedrasile Hardcore	<i>C. Sinensis</i> , Valerian, St John's wort
Zalestrim	<i>C. Sinensis</i> , Black Cohosh, Dong Quai
Slim-Citi	Hoodia
Ephedra	Mau Hang
Leptoril	<i>C. Sinensis</i> , Aspirin
Adipokinetix	<i>C. Sinensis</i>
Xenadrine	<i>C. Sinensis</i> , Ma Huang
Lipovox	<i>C. Sinensis</i>
Lean fire	<i>C. Sinensis</i>
Miracle Burn	Hoodia
7 DFB	Noni extract
Curvatrim	<i>C. Sinensis</i> , Dong Quai
Ambi-Slim	<i>C. Sinensis</i> , <i>Garcinia Cambogia</i> , Chromium, Valerian
TrimSpaX32	<i>C. Sinensis</i> , Hoodia Gordoni
Eroved	Hoodia, <i>Garcinia Cambogia</i> , Chromium
Zylorin	Hoodia, <i>C. Sinensis</i> , Chromium
Jet Fuel	<i>C. Sinensis</i> , Hoodia,
VPX redline	<i>C. Sinensis</i>
Metabolene	<i>C. Sinensis</i> , Chromium, Hoodia

warnings regarding reported cases of hepatotoxicity^[43]. Although the Usnic acid has been removed from the formulation, this diet pill still contains Norephedrine or Norphenephine and Green tea extracts. *Ephedrasil Hardcore*, a top selling diet pill, is a newer formulation of Ephedra following its ban in 2004, and contains many ingredients including Chromium, Yohimbine, and green tea extract.

Hoodia Gordoni, a popular supplement used for appetite suppression, and is derived from a cactus-like bush leaf native to southern Africa. Although initially isolated by Pfizer in the 1970s, research was discontinued due to liver toxicity found in early research studies. Despite these reports, this is a common ingredient in dietary supplements such as *Slim-Citi*, *Trim Spa X32* and *Ephedrine-P57*.

Zalestrim is another top selling supplement composed of green tea and Black Cohosh, which are described above as known sources of potential hepatotoxicity^[44-48]. It also contains *Dong Quai*, which increases prothrombin time and thereby increases bleeding risk^[49].

In summary, this case series and review of the literature highlight the potential hepatotoxicity of commonly used herbal supplements including Hydroxycut. Due to their loose regulation in the current drug marketplace, oversight of their use by physicians and regulators alike remains poor. Those supplements with potential liver toxicity are summarized in Tables 2 and 3, although further investigation is needed to better clarify the mechanisms and patterns of injury, and inform policy makers on those ingredients which require more vigorous regulation. The use of supplements is frequently not queried by physicians, and may not be reported in the same manner as prescription drugs by patients. As such, it is advisable that physicians ask specifically about the use of non-prescription drugs and supplements, warn patients with known liver disease about the potential consequences of their use, and to query patients specifi-

Table 3 Patterns of injury in herbal hepatotoxicity

	Cholestatic	Hepatocellular	Autoimmune	Fulminant failure
Atractylis				X
Gummifera ^[50]				
Black Cohosh ^[51,52]			X	X
Callilepis				X
Laureola ^[53]				
Camelia Sinensis ^[24-28]		X		X
Chapparral ^[54]	X			X
Chromium picolinate ^[18,19]		X		
Cascara	X			
Sagrada ^[55]				
Dai-Saiko-To ^[5]			X	
Garcinia Cambogia ^[7]	X	X		
Germader ^[56,57]		X		X
Greater Celadine ^[58,59]	X		X	
Jin Bu Huan ^[60]	X			
Kava ^[61-63]		X		
Noni ^[64]		X		
Paeonia ^[65]		X		
Paulina Cupana		X		
Penny Royal ^[66,67]				X
Senna ^[68]		X		
Shou wu pian ^[5]		X		
Syo-Saiko-To ^[69]	X	X		
Teucrium Polium ^[5]				X
Usnic Acid ^[70,71]		X		X
Valerian ^[72]		X		

cally about possible supplement exposure in cases of acute or chronic liver injury. Increased attention to this issue by physicians and regulatory agencies may lead to more successful efforts to decrease the burden of drug-associated liver injury in the U.S.

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